

Molecular dynamics, Langevin, and hybrid Monte Carlo simulations in multicanonical ensemble

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ABSTRACT

We demonstrate that the multicanonical approach is not restricted to Monte Carlo simulations, but can also be applied to simulation techniques such as molecular dynamics, Langevin, and hybrid Monte Carlo algorithms. The effectiveness of the methods are tested with an energy function for the protein folding problem. Simulations in the multicanonical ensemble by the three methods are performed for a penta peptide, Met-enkephalin. For each algorithm, it is shown that from only one simulation run one can not only find the global-minimum-energy conformation but also obtain probability distributions in canonical ensemble at any temperature, which allows the calculation of any thermodynamic quantity as a function of temperature.

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1. INTRODUCTION

Simulations in a system with many degrees of freedom by conventional methods such as molecular dynamics (MD) and Monte Carlo (MC) can sample only a small portion of the entire phase space, rendering the calculations of various thermodynamic quantities inaccurate. This is because the energy function has many local minima, and at low temperatures simulations will necessarily get trapped in the configurations corresponding to one of these local minima. In order to overcome this multiple-minima problem, many methods have been proposed. For instance, simulated annealing [1] is one of the most widely used algorithms to locate the global-minimum state out of the multitude of local-minimum states. The multicanonical approach [2, 3] is another powerful technique. The advantage of this algorithm lies in the fact that from only one simulation run one can not only find the energy global minimum but also calculate various thermodynamic quantities at any temperature. The method was originally developed to overcome the supercritical slowing down of first-order phase transitions,[2, 3] and it was then proposed to be used for systems that suffer from the multiple-minima problem such as spin glasses [4] and the protein folding problem.[5] The same method was later referred to as entropic sampling,[6] but the proof of the equivalence of the two methods was given to clarify the matter.[7] In the context of the protein folding problem, the effectiveness of multicanonical algorithms was compared with that of simulated annealing.[8] It was also used to study the coil-globular transitions of a model protein,[9] helix-coil transitions of amino-acid homo-oligomers,[10] and conformational sampling of a constrained peptide.[11]

In all of the previous works the multicanonical ansatz was used in the context of Monte Carlo simulations utilizing mostly the Metropolis algorithm [12] to generate a Markov chain of configurations. However, other simulation techniques such as molecular dynamics [13] are also widely used. The purpose of the present work is to demonstrate that these techniques can be used for simulations in *multicanonical ensemble*. Here, we consider three common algorithms: molecular dynamics, Langevin,[14] and hybrid Monte Carlo.[15] The performance of the algorithms are tested with the system of an oligopeptide, Met-enkephalin.

2. METHODS

2.1. Multicanonical ensemble

Simulations in the canonical ensemble at temperature T weigh each state with the Boltzmann factor

$$w_B(E, T) = e^{-\hat{\beta}E} , \quad (1)$$

where the inverse temperature is given by $\hat{\beta} = \frac{1}{k_B T}$ with Boltzmann constant k_B . This weight factor gives the usual bell-shaped canonical probability distribution of energy:

$$P_B(E, T) \propto n(E) w_B(E, T) , \quad (2)$$

where $n(E)$ is the density of states.

In the *multicanonical ensemble*, [2] on the other hand, the probability distribution of energy is *defined* to be constant:

$$P_{mu}(E) \propto n(E) w_{mu}(E) = \text{const.} \quad (3)$$

The multicanonical weight factor for each state with energy E is then given by

$$w_{mu}(E) \propto n^{-1}(E) = e^{-S(E)} , \quad (4)$$

where $S(E)$ is the microcanonical entropy (with $k_B = 1$):

$$S(E) = \ln n(E) . \quad (5)$$

With the uniform probability distribution of Eq. (3), a simulation in multicanonical ensemble leads to a 1D random walk in energy space, allowing itself to escape from any energy barrier and to explore wide range of the phase space.

Unlike in a canonical simulation, however, the multicanonical weight $w_{mu}(E)$ is not *a priori* known, and one has to obtain its estimator for a numerical simulation. Hence, the multicanonical ansatz consists of three steps: In the first step the estimator of the multicanonical weight factor $w_{mu}(E)$ is calculated (for details of the method of finding $w_{mu}(E)$ for the case of Metropolis Monte Carlo algorithm, see Refs. [3, 8]). Then one makes with this weight factor a production run with high statistics. In this way information is collected over the whole energy range. Finally, by examining the history of

this simulation, one can not only locate the energy global minimum but also obtain the canonical distribution at any inverse temperature $\hat{\beta}$ for a wide range of temperatures by the re-weighting techniques:[16]

$$P_B(E, T) \propto P_{mu}(E) w_{mu}^{-1}(E) e^{-\hat{\beta}E} . \quad (6)$$

This allows one to calculate the expectation value of any physical quantity \mathcal{O} by

$$\langle \mathcal{O} \rangle_T = \frac{\int dE \mathcal{O}(E) P_B(E, T)}{\int dE P_B(E, T)} . \quad (7)$$

In the following subsections, we describe how to implement multicanonical simulations for Langevin, molecular dynamics, and hybrid Monte Carlo algorithms.

2.2. Langevin algorithm in multicanonical ensemble

The Langevin algorithm[14] is used to integrate the following differential equation:

$$\dot{q}_i = -\hat{\beta} \frac{\partial E(q)}{\partial q_i} + \eta_i , \quad (8)$$

where q_i ($i = 1, \dots, N$) are the (generalized) coordinates of the system, $E(q)$ is the potential energy, and η_i is a set of independent Gaussian distributed random variables with a unit variance:

$$\langle \eta_i(t_l) \eta_j(t_m) \rangle = \delta_{ij} \delta(t_l - t_m) . \quad (9)$$

It can be shown that the dynamics based on the Langevin algorithm yields a canonical distribution $P_B(E, T) \propto n(E) e^{-\hat{\beta}E}$. For numerical work one integrates the above equation by discretizing the time with step Δt :

$$q_i(t + \Delta t) = q_i(t) + \Delta t \left(-\hat{\beta} \frac{\partial E(q)}{\partial q_i(t)} + \eta_i(t) \right) . \quad (10)$$

A straightforward generalization of this technique to simulations in multicanonical ensemble can be made by replacing the $\hat{\beta}E$ in Eq. (8) by the microcanonical entropy $S(E)$:

$$\dot{q}_i = -\frac{\partial S(E(q))}{\partial q_i} + \eta_i . \quad (11)$$

The above equation now describes a dynamics which will yield a *multicanonical* distribution $P_{mu}(E) \propto n(E) e^{-S(E)} = \text{const.}$ (see Eq. (4)). (A similar consideration of multicanonical Langevin algorithm is given in Ref. [17].) Hence, for actual simulations we use

the following difference equation:

$$q_i(t + \Delta t) = q_i(t) + \Delta t \left(-\frac{\partial S(E(q))}{\partial q_i(t)} + \eta_i(t) \right) . \quad (12)$$

We remark that Eq. (11) can be written as

$$\dot{q}_i = -\frac{\partial S}{\partial E} \frac{\partial E(q)}{\partial q_i} + \eta_i = -\beta(E) \frac{\partial E(q)}{\partial q_i} + \eta_i , \quad (13)$$

where $\beta(E)$ is an energy-dependent effective inverse temperature. In this notation the term “multicanonical” becomes obvious (compare Eq. (13) with Eq. (8)).

2.3. Molecular dynamics algorithm in multicanonical ensemble

The expectation value of a physical quantity \mathcal{O} is calculated by

$$\langle \mathcal{O} \rangle_T = \frac{\int Dq \mathcal{O}(q) e^{-\hat{\beta}E(q)}}{\int Dq e^{-\hat{\beta}E(q)}} , \quad (14)$$

where the integration measure is defined by $Dq = \prod_{i=1}^N dq_i$ and q_i ($i = 1, \dots, N$) are again the (generalized) coordinates of a system. $E(q)$ is the potential energy of the system. The above equation is mathematically identical with

$$\langle \mathcal{O} \rangle_T = \frac{\int Dq D\pi \mathcal{O}(q) \exp \left(-\sum_{i=1}^N \frac{\pi_i^2}{2m_i} - \hat{\beta}E(q) \right)}{\int Dq D\pi \exp \left(-\sum_{i=1}^N \frac{\pi_i^2}{2m_i} - \hat{\beta}E(q) \right)} , \quad (15)$$

where we used the notation $D\pi = \prod_{i=1}^N d\pi_i$. Identifying the auxillary variables π_i with the conjugate momenta corresponding to the coordinates q_i , we can describe our system with a Hamiltonian

$$H(q, \pi) = \frac{1}{2} \sum_{i=1}^N \pi_i^2 + \hat{\beta}E(q_1, \dots, q_N) , \quad (16)$$

where we have set all the masses m_i equal to 1 for simplicity.

The classical molecular dynamics algorithm uses the Hamilton’s equations of motion

$$\begin{cases} \dot{q}_i = \frac{\partial H}{\partial \pi_i} = \pi_i , \\ \dot{\pi}_i = -\frac{\partial H}{\partial q_i} = -\hat{\beta} \frac{\partial E}{\partial q_i} , \end{cases} \quad (17)$$

to generate representative ensembles of configurations. For numerical work the time is discretized with step Δt and the equations are integrated according to the *leapfrog* (or

other time reversible integration) scheme:

$$\begin{cases} q_i(t + \Delta t) = q_i(t) + \Delta t \pi_i \left(t + \frac{\Delta t}{2} \right) , \\ \pi_i \left(t + \frac{3}{2}\Delta t \right) = \pi_i \left(t + \frac{\Delta t}{2} \right) - \Delta t \hat{\beta} \frac{\partial E}{\partial q_i(t + \Delta t)} . \end{cases} \quad (18)$$

The initial momenta $\{\pi_i(\frac{\Delta t}{2})\}$ for the iteration are prepared by

$$\pi_i \left(\frac{\Delta t}{2} \right) = \pi_i(0) - \frac{\Delta t}{2} \hat{\beta} \frac{\partial E}{\partial q_i(0)} , \quad (19)$$

with appropriately chosen $q_i(0)$ and $\pi_i(0)$ ($\pi_i(0)$ is from a Gaussian distribution).

In order to generalize this widely used technique to simulations in multicanonical ensemble, we again propose to replace $\hat{\beta}E$ by the entropy $S(E)$ in Eqs. (17), (18), and (19) (just as we did for the Langevin algorithm). Hence, we have a new “Hamiltonian”

$$H(q, \pi) = \frac{1}{2} \sum_{i=1}^N \pi_i^2 + S(E(q)) , \quad (20)$$

and a new set of Hamilton’s equations of motion

$$\begin{cases} \dot{q}_i = \frac{\partial H}{\partial \pi_i} = \pi_i , \\ \dot{\pi}_i = -\frac{\partial H}{\partial q_i} = -\frac{\partial S(E(q))}{\partial q_i} = -\frac{\partial S}{\partial E} \frac{\partial E(q)}{\partial q_i} . \end{cases} \quad (21)$$

This is the set of equations we adopt for multicanonical MD simulations. Formally it can be understood as a rescaling of the usual force term by the derivative of the entropy. For numerical simulations the Hamilton equations are again discretized in time and integrated by a *leapfrog* scheme.

2.4. Hybrid Monte Carlo algorithm in multicanonical ensemble

The hybrid Monte Carlo algorithm[15] is based on the combination of molecular dynamics and Metropolis Monte Carlo algorithms. Namely, each proposal for the Metropolis method is prepared by a short MD run starting from the actual configuration. Hence, this algorithm is based on a global update, while in the conventional Metropolis method one is usually restricted to a local update. Furthermore, the Metropolis step ensures that the sampled configurations are distributed according to the chosen ensemble, while conventional molecular dynamics simulations are hampered by difficult-to-control systematic errors due to finite step size in the integration of the equations of motion.

Given the set of coordinates $\{q_i\}$ of the previous configuration and choosing the corresponding momenta $\{\pi_i\}$ from a Gaussian distribution, a certain number of MD steps are performed to obtain a candidate configuration $\{q'_i, \pi'_i\}$. This candidate is accepted according to the Metropolis Monte Carlo criterion with probability

$$p = \min\{1, e^{-(H(q', \pi') - H(q, \pi))}\} , \quad (22)$$

where H is the Hamiltonian in Eq. (16). The time reversibility of the *leapfrog* integration scheme ensures detailed balance and therefore convergence to the correct distribution. The whole process is repeated for a desired number of times (Monte Carlo steps). The number of integration (*leapfrog*) steps N_{LF} and the size of the time step Δt are free parameters in the hybrid Monte Carlo algorithm, which have to be tuned carefully. A choice of too small N_{LF} and Δt means that the sampled configurations are too much correlated, while too large N_{LF} (or Δt) yields high rejection rates. In both cases the algorithm becomes inefficient.

The generalization of this technique to simulations in multicanonical ensemble can again be made by replacing the Hamiltonian of Eq. (16) with the multicanonical Hamiltonian of Eq. (20), i.e., replacing $\hat{\beta}E$ by the entropy $S(E)$ in the equations of motion.

3. RESULTS AND DISCUSSION

The effectiveness of the algorithms presented in the previous section is tested for the system of an oligopeptide, Met-enkephalin. This peptide has the amino-acid sequence Tyr-Gly-Gly-Phe-Met. The potential energy function that we used is given by the sum of electrostatic term, Lennard-Jones term, and hydrogen-bond term for all pairs of atoms in the peptide together with the torsion term for all torsion angles. The parameters for the energy function were adopted from ECEPP/2.[18]-[20] The computer code SMC [21] was modified to accomodate the multicanonical ensemble.

For the coordinates $\{q_i\}$ we used the dihedral angles. (We remark that it was recently claimed that convergence is faster for the dihedral coordinates.[22] Of course we could have used Cartesian coordinates as well with the same set of equations.) The peptide-bond dihedral angles ω were fixed to be 180° for simplicity. This leaves 19 dihedral angles as generalized coordinates. By definition of multicanonical ensemble, one cannot obtain

information on the real dynamics of the system by the MD algorithm, and only static thermodynamic quantities can be calculated. For this reason we do not need to consider the equations of motion for dihedral space as presented in Ref. [23], but can use the much simpler form as given in the previous section. However, we remark that this may not be the optimal choice. Very often it may be more suitable to distinguish between “soft” and “hard” degrees of freedom and introduce appropriately chosen “masses” in the equations of motion.[22]

For the multicanonical MD simulations, we made a single production run with the total number of time steps $N_{LF} = 400,000 * 19$ and the time-step size $\Delta t = 0.005$ (in arbitrary units), after the optimal estimate for the multicanonical weight factor $w_{mu}(E)$, or entropy $S(E)$, was obtained. For the multicanonical Langevin algorithm, a production run with the same number of time steps ($N_{LF} = 400,000 * 19$) as in the MD simulation, but our optimal time-step size was only $\Delta t = 0.0001$. This indicates that the simulation moves more slowly through phase space, and we expect slower convergence to the multicanonical distribution than in MD case. For the multicanonical hybrid Monte Carlo algorithm, an MD simulation with 19 leapfrog steps was made for each Monte Carlo step and a production run with 200,000 MC steps was made. Since the Metropolis step in hybrid Monte Carlo corrects for errors due to the numerical integration of the equation of motion, the time-step size can be large for this algorithm. We chose $\Delta t = 0.01$ in our units. The initial conformation for all three simulations was the final (and therefore equilibrated) conformation obtained from a multicanonical Monte Carlo simulation of 200,000 sweeps, following 1,000 sweeps for thermalization with the same weights (in each sweep all of the 19 angles were updated once).

In Fig. 1 the time series of the total potential energy are shown for the three multicanonical simulations. They all display a random walk in energy as they should for a simulation in multicanonical ensemble. All the lowest-energy conformations were essentially the same (with only a small amount of deviations for each dihedral angle) as that of the global-minimum energy conformation previously obtained for the same energy function (with $\omega = 180^\circ$) by other methods.[24, 5, 25] The global-minimum potential energy value obtained by minimization is -10.7 kcal/mol.[25] The random walks of the

MD and hybrid MC simulations visited the global-minimum region ($E < -10$ kcal/mol) three times and five times, respectively, while that of the Langevin simulation reached the region only once. These visits are separated by the walks towards the high energy region much above $E = 16$ kcal/mol, which corresponds to the average energy at $T = 1000$ K.[5]

In Fig. 2a the time series of the end-to-end distance r is plotted. Here, the distance was measured from N of Tyr 1 to O of Met 5. Only the result from the multicanonical hybrid Monte Carlo simulation is given, since the other two simulations give similar results. Note that there is a positive correlation between potential energy E and end-to-end distance r (compare Figs. 1c and 2a), indicating that a folded structure generally has a lower potential energy than a stretched one. This becomes even clearer in Fig. 2b, where we display the average end-to-end distance r as a function of potential energy E .

In Fig. 3 we demonstrate that the probability distribution $P_{mu}(E)$ of potential energy E obtained from the multicanonical MD simulation is essentially flat (of the same order of magnitude) over the whole energy range. Similar figures can be drawn for the other two algorithms.

In Fig. 4 the entropy $S(E)$ calculated from the probability distribution $P_{mu}(E)$ is displayed (see Eqs. (3) and (4)). Only the result from multicanonical MD simulation is given, since the other two simulations give essentially the same results. It is a monotonically increasing function. Note that there is a sudden drop of $S(E)$ near $E = -10$ kcal/mol, suggesting that the global-minimum conformation is “unique”.

Simulations in multicanonical ensemble can not only find the energy global minimum but also any thermodynamic quantity as a function of temperature from a single simulation run. We have calculated the specific heat and average potential energy as functions of temperature for the three algorithms. The results all agreed within errors with those from our previous multicanonical MC runs (see, for instance, Refs. [5, 8]). Here, we just show another example of such a calculation, the average end-to-end distance as a function of temperature. The results are essentially the same for the three algorithms. That from multicanonical Langevin algorithm is shown in Fig. 5. We see that the average end-to-end distance becomes smaller as the temperature is lowered, indicating that the peptide has a compact structure at low temperatures.

CONCLUSIONS

In this article we have shown that the multicanonical ansatz is not restricted to Monte Carlo simulations, but can also be used in combination with other simulation methods such as molecular dynamics, Langevin, and hybrid Monte Carlo algorithms. We have tested the performances of these three methods in multicanonical ensemble for a simple peptide, Met-enkephalin. The results were comparable to those of the original Monte Carlo version.[5] We believe that there is a wide range of applications for multicanonical versions of molecular dynamics and related algorithms. For instance, multicanonical MD simulations may prove to be a valuable tool for refinement of the protein structures inferred from X-ray and/or NMR experiments.

Acknowledgements:

The authors thank A. Kidera and N. Nakajima for informing us that they have also developed a method for implementing an MD algorithm in multicanonical ensemble. We are grateful to F. Hirata for letting us know the existence of Refs. [17, 23]. Our simulations were performed on the computers of the Computer Center at the Institute for Molecular Science, Okazaki, Japan. This work is supported, in part, by the Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports, and Culture.

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FIGURE CAPTIONS:

FIG. 1. (a) Time series of the total potential energy E from a multicanonical Langevin simulation of $400,000 \times 19$ time steps with step size $\Delta t = 0.0001$. (b) Time series of E from a multicanonical molecular dynamics simulation of $400,000 \times 19$ time steps with step size $\Delta t = 0.005$. (c) Time series of E from a multicanonical hybrid Monte Carlo simulation of 200,000 MC steps. For each MC step an MD run of 19 time steps was made with step size $\Delta t = 0.01$.

FIG. 2. (a) Time series of end-to-end distance r from the multicanonical hybrid Monte Carlo simulation. (b) The average end-to-end distance r as a function of potential energy E obtained from the multicanonical hybrid Monte Carlo simulation.

Fig. 3. Probability distribution of potential energy E obtained from the multicanonical molecular dynamics simulation.

Fig. 4: Microcanonical entropy $S(E)$ as a function of potential energy E obtained from the multicanonical molecular dynamics simulation.

FIG. 5: The average end-to-end distance r as a function of temperature obtained from the multicanonical Langevin simulation.